REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-12 are under consideration in the instant application. These claims were subject to a restriction requirement, in response to which, Applicants elected, with traverse, to prosecute the claims of Group I (*i.e.*, claims 1-5, 7 and 8). The restriction requirement was made final and hence claims 6 and 9-49 were withdrawn from consideration. Claims 1-5, 7 and 8 stand variously rejected under 35 U.S.C. §112, first and second paragraphs. The office action further articulated a number of objections to the specification. Applicants respectfully traverse the rejections, and provide the following remarks for the Examiner's consideration. Applicants respectfully request reconsideration of the rejections in view of this response.

II. Response to Objections to Informalities in the Claims and the Specification

The Examiner objected to the drawings for referring to sequence identification information without designating a SEQ ID NO: and because all of the drawing sheets were not the same size. Attached herewith is a clean set of formal drawings all presented on a uniform size paper.

The Examiner objected to the specification for failing to identify appropriate sequence identification numbers. Applicants present the above amendment to address this objection. The above amendment also addresses the objections to claims 1-5, 7 and 8, by removing from the claims subject matter that has been withdrawn as non-elected. Applicants reserve the right to prosecute this withdrawn subject matter at a later date.

III. Response to rejection under 35 U.S.C. §112, second paragraph

Claim 7 was rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. More particularly, the claim 7 was rejected for reciting the term "stringent" conditions. The Office Action states that "the specification does not define what conditions

constitute 'stringent.' While page 21 of the specification describes some conditions which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of the term." Applicants traverse the rejection and provide the following comments for the Examiner's consideration.

At MPEP § 2173.02 it is stated that:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

Moreover, the MPEP guides that breadth of claim is not to be equated with definiteness (MPEP 2173.04). The Examiner admits that page 21 of the specification provides exemplary guidance to those of skill in the art of what is intended by the term stringent conditions. Moreover, term "stringent conditions" is a term of art well recognized by those of skill, and given the guidance presented in the specification, Applicants submit that the claim is sufficiently clear to apprise those of skill as to the scope of the claim.

Furthermore, as additional exemplary evidence that the term "stringent conditions" is a term of art readily accepted and used by those of skill in the art, Applicants have attached herewith copies of U.S. Patent No. 6,444,456; U.S. Patent No. 6,436,687; U.S. Patent No. 6,416,986 and U.S. Patent No. 6,387,688. Each of these patents was issued within the last twelve months and provides claims analogous to claim 7 of the present invention. The specifications of these patents do not provide a description of "stringent conditions" that is as detailed as the present application. In addition, Applicants submit that United States Patent and Trademark Office's Written Description guidelines use the phrase "nucleic acid that specifically hybridizes under highly stringent conditions" and claim 7 in the present application is presented

using the same language as suggested in that example.

In light of the above remarks, Applicants submit that those of skill in the art would understand the subject matter intended to be within the scope of claim 7, without the need for introducing additional conditions into the claim from the specification. Applicants believe the above remarks remove the grounds for rejection of claim 7 based on 35 U.S.C. §112, second paragraph. Applicants request withdrawal of the rejection and reconsideration of the application in light of this response. Should the Examiner have any further questions regarding this rejection or the Applicants' response thereto, Applicants respectfully request that the Examiner contact the undersigned representative to facilitate a speedy resolution of such queries

IV. Response to rejection under 35 U.S.C. §112, first paragraph for lack of written description.

Claims 1-3, 5, 7 and 8 were rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

Briefly reiterating the rejection, the Office Action states that the specification "only provides a single representative species comprising SEQ ID NO:79 encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these polypeptides." (Office Action, paper 9, page 9). Applicants respectfully traverse the rejection.

Throughout the specification, Applicants have provided detailed descriptions of the caspases intended to be encompassed by the claimed invention. At page 1, line 18 through page 2 line 3, the specification teaches that caspases are initially expressed as zymogens and that caspases comprises a pentapeptide which contains the catalytic cysteine. Other domains such as the caspase-recruiting domains (CARD), death effector domains (DED) also are discussed (Specification, page 2, lines 4-12). In addition, the specification provides details of caspase

activities that the proteins of the claimed invention should possess. In light of these specific disclosures in the specification, those of skill in the art would have understood that Applicants were in possession of the claimed invention.

However, in order to expedite prosecution, Applicants have amended each of claims 1 through 3 to recite "wherein said polypeptide comprise a QACXG domain." Those of skill in the art would understand the caspase proteins possessing such a domain comprise the catalytic cysteine of caspases.

Applicants thank the Examiner for referring Applicants to the written description guidelines. In reviewing the revised interim guidelines. The Guidelines suggest that where a review of the content of the specification provides a description of a protein having a given sequence or variants having a percentage identity to that sequence, such compositions may be claimed using the "product by function" format exemplified in Example 14. The Guidelines themselves teach that "procedures for making variants of SEQ ID NO:3 [*i.e.*, the sequence described in Example 14 of the Guidelines] are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Applicants believe that claims 1-3 of the present application conform to the language suggested in Example 14 of the Guidelines in that claim 1 identifies a sequence (i.e., SEQ ID NO:77), claim 1 identifies the percentage homology (98%) and claim 1 also provides the catalytic activity that the proteins being claimed must possess and that the proteins must possess a specific catalytic cysteine residue. As indicated in the Guidelines, this claim encompasses two different generic embodiments, the first being a protein which comprises SEQ ID NO:77 and the second being variants of SEQ ID NO:77. The specification expressly reduces to practice the species SEQ ID NO:77 and as discussed below various variants thereof also. It is not essential to provide a specific working example of all other species "since all of the variants must possess the specified catalytic activity and must have at least" (Guidelines page 54) 98% structural identity with the reference compound and because of the presence of various assays which Applicants

have provided for identifying all of the at least 99% identical variants of SEQ ID NO: 77 that are capable of the specified caspase activity. One of skill in the art would conclude that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Applicants submit that given the description provided in the specification, the United States Patent and Trademark Office's own guidelines compel a conclusion that "disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention." (see Guidelines, conclusion to Example 14, page 54). As such Applicants request that the rejection of claims 1-3, 5, 7 and 8 under 35 U.S.C. §112, first paragraph for lack of written description be withdrawn, and the claims should be reconsidered for allowance.

V. Response to rejection under 35 U.S.C. §112, first paragraph for lack of enablement.

Claims 1-3, 5, 7 and 8 were rejected under 35 U.S.C. §112, first paragraph, because it is alleged that the "specification, while being enabling for a caspase polypeptide comprising the amino acid sequence of SEQ ID NO:7[7], does not reasonably provide enablement for any caspase polypeptide comprising an amino acid sequence at least 98% identical to 30 contiguous amino acids of SEQ ID NO:7[7]." Applicants respectfully traverse the rejections and request reconsideration in light of the following comments.

The claims of the present invention are directed to novel caspase proteins, the claims recite the sequence of the claimed caspase proteins, and the specification recites that the caspase proteins comprise a QACXG sequence which contains the catalytic cysteine residue present in standard caspase proteins. Figure 4 of the specification and page 91, lines 7-9 provides a description of the alignment of the amino acid sequence of a polypeptide of SEQ ID NO:77 with other caspases. Figure 5 shows a comparison of the sequences of representative human caspase species related to SEQ ID NO:77. The regulatory CARD domain, large and small subunits, and active site residues of a number of caspase isoforms are identified in the Table bridging pages 23-25 and shown in the figure legend to Figure 5. Example 3 (pages 94-99) of the specification

describes in detailed strategy for cloning and expressing an active caspase-12 protein in both mammalian and bacterial cells. Additionally, a variant without the regulatory CARD domain (ΔCARD) also is described (SEQ ID NOS: 78 and :79) in that Example. Example 5 (pages 104-107) of the specification describes an evaluation of protease activity of recombinant human caspase-12 (SEQ ID NO:77) isolated from bacteria. Page 105, line 24, presents a teaching that caspase-3 is a substrate of representative initiator caspases –8 and-9. Activation of caspase-3 is indicated by the appearance of the p19, large subunit of the active enzyme. Using this methodology, the inventors demonstrated the proteolytic activity of recombinant human caspase-12 (SEQ ID NO:77) against the substrate, procaspase-3. Additionally, the inventors demonstrated that the variant that lacks the regulatory domain (ΔCARD) also retains enzymatic activity against procaspase-3 (see Figure 8). From these teachings, one of skill in the art would be able to produce a variant of a caspase of SEQ ID NO:77 without undue experimentation.

Moreover, as taught in the specification, the enzymatic activity of recombinant human caspase-12 isolated from bacteria may be measured using a standard caspase activity assay (page 107, line 9-21). The description of these assays and results shows one of skill in the art how to determine whether a given protein possesses caspase-specific, proteolytic activity. This activity is shown not only for the polypeptide of SEQ ID NO:77, but also for the ΔCARD (SEQ ID NO:78) variant lacking the CARD prodomain. Hence, the specification has taught those of skill in the art how to make the claimed protein compositions.

Applicants disagree with the Examiner that the application fails to provide guidance as to which regions may be modified without affecting caspase activity. The specification expressly teaches the use of mammalian cell expression systems to show that both the wild-type and ΔCARD variant were activated similarly, as evidenced by the disappearance of the proenzyme, through α-FAS-induced programmed cell death (see Specification p. 109, line 15 through p. 110 line 7; Figure 9). These studies demonstrate that the CARD region of caspase 12 may be removed, with the resultant protein retaining caspase activity. The specification expressly teaches one of skill in the art how to determine whether such a caspase can serve as a substrate for calpain, an enzyme known to activate murine caspase-12 (see specification p. 112,

line 20-p. 114, line 5). Thus, the specification demonstrates that the protein may be modified, and teaches a specific example of such a modified protein which nonetheless retains activity, and further teaches how one of skill in the art can determine whether the resultant modified protein still retains caspase activity. The teachings of the activity of the ΔCARD variant in the specification also provides the requested support for the "general tolerance of the claimed caspase to modification and extent of such tolerance."

Moreover, while it is true that not all of the factors need to be addressed, the remaining *Wands* factors argue in favor of enablement. Contrary to the Examiner's assertions, the above discussion points to various teachings in the specification that show working examples of at least one variant of the caspase of SEQ ID NO:77. The nature of the claimed invention is one in which the level of skill of the ordinary artisan is high. The field of the invention is protein/enzyme compositions, more specifically, the claims of the application are directed to caspase-12 and variants thereof. Caspase 12 is a member of a large family of caspases. This family of enzymes have been known since 1992 (*e.g.*, see Thornberry *et al.*, *Nature* vol. 356(6372):768-774, 1992), and the structure/function relationships of the various members of this family have been well characterized (see e.g., U.S. Patent No. 6,087,150, which is directed to caspase-7; U.S. Patent No. 5,786,173 for a description and claims directed to caspase-8 (Mch5) and caspase-10 (Mch4); U.S. Patent No. 6,455,296 for caspase-9; and U.S. Patent No. 6,432,628 for caspase-14.)

Given that caspases have been studied for eleven years and that the conserved domains of these proteins are well known to those of skill in the art, Applicants submit that there is a sufficiently high degree of predictability in the field of producing caspase variants. The specification at pages 48-49 provides Tables A-C showing exemplary conservative amino acid substitutions. Those of skill in the art would readily understand that it would be desirable to produce conservative substitutions in the sequence of SEQ ID NO:77, such that caspase activity is retained. Figure 5 shows a comparison of caspase 12 with various other members of the caspase family. The various domains of the caspases are identified in the Figure and throughout the specification. As such, one of skill in the art could simply refer to Figure 5, and the Tables in

the specification to produce conservative variants of the sequence of caspase-12. As recombinant techniques for producing such variants were common-place and routine at the time the instant application was filed, no undue experimentation would be required to produce such variants.

In light of the above comments, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

VI. Concluding Remarks.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

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Respectfully submitted,

By _____

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